REMARKS

Claims 1-14, 22, and 23 are pending in the application. Claims 14, 22, and 23 were withdrawn from consideration, leaving claims 1-13 subject to examination. Claims 1-3, 6, and 8-13 remain rejected under 35 U.S.C. § 102(e), and claims 1, 3-5, 6, 7, 10, 11 remain rejected under 35 U.S.C. § 103(a). Each of the rejections is addressed below.

First, Applicants note that, in the interest of expediting prosecution, the claims have been amended to focus on specific aspects of the invention. In particular, claim 1 has been amended to delete reference to prevention of metastasis, which could be interpreted as covering destruction of residual cells at the site of surgical resection. The claims thus now specify that the method is for treating (rather than preventing or treating) metastasis of cancer. A metastasis is, by definition, at a site that is removed from the site of the tumor from which it originated. Thus, treatment of metastasis means treatment away from the site of resection.

Second, Applicants note the addition of new claim 28, which specifies a method of treating regional lymphatic metastases involving surgical resection of a tumor and administration of an attenuated, replication-competent herpes virus to the site of resection. Support for this amendment can be found throughout the application, for example, in claims 1, 4, and 5, as well as at page 3, lines 5-7 of the application as filed (paragraph 0007 of the U.S. publication). No new matter is added by this amendment. Further, this claim is within the present restriction group, as it essentially combines claims that are within the present restriction group.

Third, Applicants note that the Examiner requires that non-elected claims be canceled in replying to the final Office Action. Applicants request that this requirement be reconsidered because, as is discussed below, the claims of Groups I and II define a technical feature linking the

inventions of these groups, which defines a contribution over US 2002/0071832. This is discussed in more detail below, in connection with the rejection under 35 U.S.C. § 102(e) over the cited reference, over which the present invention is novel, thus defining a contribution over the prior art. Applicants thus again request reconsideration of the Restriction Requirement. Applicants further note that each of the claims of both Groups I (claims 1-13) and II (claims 14, 22, and 23) are readable on the elected species.

The rejections in the Office Action are each addressed, as follows.

Rejections under 35 U.S.C. § 102(e)

Rejection over Fong et al., US 2002/0071832

Claims 1, 2, 6, and 8-13 remain rejected under 35 U.S.C. § 102(e) as being anticipated by Fong et al., US 2002/0071832, with the Examiner stating "...the material and method step(s) recited in the Fong [publication] are the same material and method step(s) recited in the claimed method... There is nothing in the recited method steps or material used that differentiates the claimed invention from the method taught in the prior art" (page 3; citations omitted). Applicants respectfully request that this rejection, in view of the present amendments.

It is established in the law that "[n]ew uses of known products or processes are indeed patentable subject matter" (emphasis added; citations omitted; but see, e.g., 35 U.S.C. § 101; *In re King*, 801 F.2d 1324 (Fed. Cir. 1986); and *Perricone v. Medicis Pharmaceutical Corp.*, 432 F.3d 1368 (Fed. Cir. 2005)).

The Fong publication suggests the use of surgery to remove a tumor and inoculation of viruses into the resection site, to ensure destruction of any remaining tumor cells (paragraph 0036

of Fong). Thus, the purpose of the method proposed in the Fong publication is to destroy tumor cells at the site of resection. In contrast, the present claims, as now amended, specify the treatment of metastases, which, by definition, are not at the site of resection. Although the present methods involve surgical excision of tumors and administration of viruses to resection sites, similar to the cited method proposed in the Fong publication, these steps are carried out for different purposes: treatment of metastases (the present application) vs. destruction of resection site tumor cells (the Fong publication). Thus, the present invention can be viewed as a new use of a known process, which, as noted above, represents patentable subject matter.

Applicants further submit that the methods of the present claims provide treatment options for patients for whom treatment regimens based solely on surgical excision of tumors and destruction of tumor cells in the tumor bed would not have been considered sufficient. For example, treatment of tumors found to have metastasized (e.g., by lymph node analysis) or tumors having a high propensity to metastasize would not be effectively treated by an approach focusing only on the site of excision. Applicants thus submit that the present method is not inherent in the cited method of the Fong publication, as that method would clearly be used in the case of local treatment, while the present method can be used to treat metastases.

The present claims, as amended, thus specify a new, different use for a process involving tumor excision and virus administration to the site of resection. The cited method of the Fong publication is proposed for use in the context of local therapy, to destroy any remaining tumor cells at the site of resection. Such an approach would not be selected for use in patients in whom metastasis has already occurred, or patients having tumors at high risk of metastasis, as killing remaining tumor cells at the site of resection would not be enough. Thus, the methods of the

present invention and the cited method of the Fong publication are for use for distinct purposes, and the presently claimed method thus is a new use, and thus is patentable.

Applicants further note that dependent claims 4 and 5 specify that the cancer metastasis is in the lymphatic system (claim 4), such as in a lymph node (claim 5), and that new independent claim 28 specifies that the cancer is a regional lymphatic metastasis. Treatment of such metastases by administration of a virus to a site of tumor resection certainly represents a new use of a method including tumor excision and virus administration to the excision site, and can be used with a very select patient population that certainly would not be treated with local methods alone.

Applicants further submit that natures of the targeted cells of the method of the present claims and that of the cited method of the Fong publication differ as well. In particular, tumors having metastatic potential generally are highly heterogeneous, and it is only certain cells within such tumors that have the capability to successfully form metastases, due to their unique abilities to overcome substantial obstacles to metastasis (see, e.g., Fiddler et al., Hospital Practice, July 1982, p. 57-64; a copy was enclosed in Applicants' previous reply). For example, such cells must detach from a primary tumor, gain entrance into circulation, survive in circulation, arrest at an organ capillary bed, extravasate, and grow in a new site, all the while evading host inflammatory and immune system mediators (Fiddler et al., supra). Most cells within a tumor do not undergo such actions.

Further, it has been reported that tumor cells that form viable metastases may represent 1% or less of tumor cells that leave the site of a primary tumor (Schirrmacher, Advances in Cancer Research 43:1-64, 1985; a copy was enclosed with Applicants' prior reply). Thus, only a

fraction of the cells of a primary tumor leave the tumor, and only a very small portion of these leaving cells form viable metastases. It thus follows that most cells within a tumor do not and likely cannot form metastases. It is these latter cells that are the target of the method mentioned in the cited reference: cells that may, if left in the tumor bed, continue to grow and form another tumor at the site of resection. The other, more specialized and rare cells, which may form metastases (and which are the subject of the present claims), are not mentioned in the cited reference.

In view of the above, Applicants submit that the presently claimed methods are different from the cited method of the Fong publication, and thus that the present rejection should be withdrawn.

Rejection over Molnar-Kimber et al., U.S. Patent No. 6,428,968

Claims 1-3, 6, 8, 9, 12, and 13 remain rejected under § 102(e) as being anticipated by Molnar-Kimber et al., U.S. Patent No. 6,428,968. The Examiner maintains that this reference teaches the same materials and steps as are used in the claimed method. Applicants disagree.

This rejection must be withdrawn, because Molnar-Kimber simply does not teach the same materials and steps as are used in the present claims (not to mention use of these materials and steps for the purpose for which presently claimed methods are used). Focusing first on the fact that Molnar-Kimber does not teach the materials and steps of the present claims, Applicants note that Molnar-Kimber does not describe administration of virus to sites of surgical resection. Rather, Molnar-Kimber suggests administration of oncolytic viruses, generally, and notes that treatments "supplemental treatments [i.e., treatments supplemental to oncolytic virus therapy]

may remain necessary to prevent re-establishment of nearly ablated tumors, to kill residual tumor cells following surgical tumor excision, and to inhibit growth of immature metastases by killing tumor cells distributed throughout the body of a subject" (emphasis added; column 2, lines 49-56). Molnar-Kimber nowhere states that oncolytic virus therapy should be used as the "supplemental treatment" to address the latter issues, and use of such therapy is inconsistent with the fact that the "supplemental treatment" is carried out to supplement oncolytic virus treatment. Further, the only instances in which Molnar-Kimber provides any specific guidance as to how virus should be administered, the approaches are by intratumoral injection (column 4, lines 66-67, column 5 line 6, column 10, line 58, column 19 line 33-34, column 20, line 48) or local administration to the tumor (column 2, lines 44-45).

In their prior reply, Applicants note that this discussion of Molnar-Kimber is in the section of the patent describing the problems of the state of art, and is not proposing any solutions to such problems. In the present Office Action, the Examiner addresses this prior submission by stating "...the use of patents as references is not limited to what the patentees describe as their own inventions or to the problems with which they are concerned. They are part of the literature of the art, relevant for all they contain" (citations omitted). In response, Applicants note that they did not dismiss the cited passage of Molnar-Kimber because it was characterizing the prior art. Rather, this fact was mentioned to put the passage in a context: Molnar-Kimber was characterizing a problem in the prior art and did not propose a solution to the problem. Molnar-Kimber did not propose a solution to the problem, whether the solution be another prior art approach or an approach that is part of the invention of Molnar-Kimber. Molnar-Kimber simply did not propose a solution to the problem.

Thus, the Molnar-Kimber patent does not describe the presently claimed invention, and the present rejection should therefore be withdrawn.

Rejections under 35 U.S.C. § 103(a)

Rejection over Fong et al., US 2002/0071832, in view of Wong et al., Human Gene Therapy 12(3):253-265, 2001

Claims 1, 6, and 7 were rejected for obviousness over Fong et al., US 2002/0071832, in combination with Wong et al., Human Gene Therapy 12(3):253-265, 2001. This rejection is respectfully traversed.

The Fong publication is cited for teaching administration of herpes simplex virus to the site of resection of a tumor, as noted above. The Examiner states "destruction of any remaining tumor cells would read on the preamble of the claim because destruction of remaining tumor cells would prevent tumor cells from metastasizing from the tumor bed." The Wong reference is cited for teaching herpes simplex virus NV1023. The Examiner concludes that it would have been obvious to use NV1023, as taught by Wong, in the method of Fong, because Wong teaches that NV1023 is an attenuated, replication-competent, oncolytic herpes simplex virus. Applicants respectfully disagree with this rejection.

As discussed above, the present claims now specify the treatment of metastases (such as lymphatic metastases), rather than the prevention or treatment of metastases. Also as discussed above, the cited method of the Fong publication does not teach the treatment metastasis. Rather, the cited method of Fong is suggested for the destruction of tumor cells at the site of resection, to prevent re-growth of tumor cells and reformation of a tumor at the site of resection. This is very

different from the presently claimed invention, in which the focus is not the activity of administered virus at the site of resection, but at distal sites to which certain tumor cells may have migrated and not tumor cells as they remain at the surgical site. As is discussed in detail above, tumors including cells that have the potential to metastasize are highly heterogeneous, and from such tumors it has been reported that only 1% or less of even the cells that leave the primary tumor site survive to become viable metastases (Fidler, supra; Schirrmacher, supra). Thus, the mention of virus administration to a surgical bed in the Fong publication does not provide any suggestion or motivation to treat metastases, which is the focus of the present claims. Indeed, prior to the present invention, the activity of herpes simplex viruses in treating metastases was not known or predictable, and no references have been cited to conclude otherwise. Thus, it would not have been obvious to use any herpes simplex virus, not to mention NV1023, in a method for preventing or treating metastasis at a distal site. Applicants thus request that this rejection be withdrawn.

Rejection over Molnar-Kimber et al., U.S. Patent No. 6,428,968, in view of Wong et al., Human Gene Therapy 12(3):253-265, 2001

Claims 1, 6, 7, 10, and 11 remain rejected under § 103(a) for obviousness over Molnar-Kimber et al., U.S. Patent No. 6,428,968, in combination with Wong et al., Human Gene Therapy 12(3):253-265, 2001. This rejection is respectfully traversed.

The Examiner states that the Molnar-Kimber patent teaches killing tumor cells by administration of herpes simplex viruses and chemotherapeutic agents, and that such a method can be used following surgical excision or for inhibiting growth of immature metastases by

killing tumor cells distributed throughout the body, as is noted above. The Wong reference is cited for teaching herpes simplex virus NV1023. The Examiner concludes that it would have been obvious to use NV1023, as taught by Wong, in the method of Molnar-Kimber, because Wong teaches that NV1023 is an attenuated, replication-competent, oncolytic herpes simplex virus. Applicants respectfully disagree with this rejection.

As is discussed above in reference to the rejection under § 102(e) over Molnar-Kimber, the cited patent does not describe the administration of herpes simplex viruses to the of site surgical resection to prevent or treat cancer metastasis. Rather, as is discussed above, the passage cited by the Examiner on this point (column 2) describes a study of intraperitoneally administered herpes virus, and notes that because residual tumor cells remain after such treatment, some type of unspecified, "supplemental" treatments may be required for effective treatment. Thus, similar to the Fong reference, discussed above, Molnar-Kimber does not suggest or provide motivation for the administration of a herpes virus to the site of surgical resection, not to mention NV1023. This rejection should therefore be withdrawn.

Rejection over Cole et al., U.S. Patent No. 5,162,231, in combination with Molnar-Kimber et al., U.S. Patent No. 6,428,968, and Johnston et al., Ann. Thorac. Surg. 71:1120-1125, 2001

Claims 1, 3, and 5 remain rejected for obviousness over Cole et al., U.S. Patent No. 5,162,231, in combination with Molnar-Kimber et al., U.S. Patent No. 6,428,968, and Johnston et al., Ann. Thorac. Surg. 71:1120-1125, 2001.

The Cole patent is cited for teaching the recurrence of malignant lesions or metastasis in lung cancer, even after surgical resection. The Examiner cites the Molnar-Kimber patent in this

rejection, stating that it teaches herpes simplex virus administration following surgical excision, and thus use of this method for enhancing the treatment of lung cancer. The Johnston reference is cited for teaching that lung tumors spread to lymph nodes. The Examiner states that it would have been obvious to combine the teachings of these references to enhance the treatment of resected lung cancer in a patient. Applicants disagree.

As is noted above, the Molnar-Kimber patent does not teach administration of herpes simplex viruses to the site of surgical excision. Rather, the only particular mode of adminstration mentioned by Molnar-Kimber is intratumoral injection. The only mention in Molnar-Kimber of residual cancer cells present in a site of tumor resection is in noting that some type of unspecified, "supplementary" treatment may be required to address such cells in the context of administration of a herpes simplex virus administered by intraperitoneal injection to treat malignant mesothelioma. Molnar-Kimber does not even suggest that such treatment should involve administration of a virus to the resection site. Neither of the other cited references suggests or provides motivation for administration of a herpes simplex virus to the site of tumor resection. Applicants thus submit that this rejection should be withdrawn.

CONCLUSION

Applicants submit that the claims are in condition for allowance, and such action is respectfully requested. Although no charges are believed to be due, if there are any charges or any credits, please apply them to Deposit Account No. 03-2095.

Respectfully submitted,

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